Illicit and pharmaceutical drug consumption estimated via wastewater analysis. Part A: Chemical analysis and drug use estimates

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Abstract

This paper presents, for the first time, community-wide estimation of drug and pharmaceuticals consumption in England using wastewater analysis and a large number of compounds. Among groups of compounds studied were: stimulants, hallucinogens and their metabolites, opioids, morphine derivatives, benzodiazepines, antidepressants and others. Obtained results showed the usefulness of wastewater analysis in order to provide estimates of local community drug consumption. It is noticeable that where target compounds could be compared to NHS prescription statistics, good comparisons were apparent between the two sets of data. These compounds include oxycodone, dihydrocodeine, methadone, tramadol, temazepam, diazepam. Whereas, discrepancies were observed for propoxyphene, codeine, dosulepin and venlafaxine (over-estimations in each case except codeine). Potential reasons for discrepancies include: sales of drugs sold without prescription and not included within NHS data, abuse of a drug with the compound trafficked through illegal sources, different consumption patterns in different areas, direct disposal leading to over estimations when using parent compound as the DTR and excretion factors not being representative of the local community. It is noticeable that using a metabolite (and not a parent drug) as a biomarker leads to higher certainty of obtained estimates. With regards to illicit drugs, consistent and logical results were reported. Monitoring of these compounds over a one week period highlighted the expected recreational use of many of these drugs (e.g. cocaine and MDMA) and the more consistent use of others (e.g. methadone).

Keywords: wastewater analysis, sewage epidemiology, illicit drugs, pharmaceuticals, consumption

1.1 Introduction

An innovative method of estimating drug consumption utilising the measuring of drug residues in wastewater was initially proposed by Daughton in 2001 (Daughton 2001), implemented by Zuccato et al. in 2004 (Zuccato, Chiabrando et al. 2005) and followed by others (Bones, Thomas et al. 2007, Huerta-Fontela, Galceran et al. 2008, Banta-Green, Field et al. 2009, Kasprzyk-Hordern, Dinsdale et al. 2009, Mari, Politi et al. 2009, van Nuijs, Pecceu et al. 2009, Karolak, Nefau et al. 2010, Metcalfe, Tindale et al. 2010, Postigo, de Alda et al. 2010, Terzic, Senta et al. 2010, Harman, Reid et al. 2011, Irvine, Kostakis et al. 2011). The first European monitoring programme was undertaken in 2010 (Thomas, Bijlsma et al. 2012). The specific details of this approach are discussed in three review articles (Postigo, Lopez de Ada et al. 2008, Zuccato, Chiabrando et al. 2008, van Nuijs, Castiglioni et al. 2010).

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The method assumes that drugs, after they are consumed and metabolised in the human body, are excreted into the sewage system as parent compounds and metabolites. These residues reach the WWTP where the wastewater is sampled before treatment. The metabolic pathways of many drugs of abuse are understood, with several metabolites known in many cases. Therefore, this approach assumes that the measured residue concentrations present in sewage can be correlated with the amount of drug consumed by a population served by a WWTP. Obvious parameters required to calculate such usage on this scale include: (a) the concentration of suitable target species in wastewater; (b) the flow rate of sewage through the WWTP at/across the time of sampling (c) the percentage of drug excreted as the selected drug target residue (DTR); and (d) the population served by the WWTP. This approach offers significant opportunities to aid in the monitoring of drug usage at a community level, however to date this concept has received relatively little validation. This paper presents, for the first time, the results of estimation of drug and pharmaceuticals consumption in England using wastewater analysis and a large number of compounds. Estimation of uncertainty for this study is a subject covered in the sister paper entitled 'Illicit and pharmaceutical drug consumption estimated via wastewater analysis. Part B: Accounting for the multiple sources of uncertainty' by H E Jones, M Hickman, A E Ades, N J Welton, D Baker and B Kasprzyk-Hordern.

1.2 Experimental

1.2.1 Sampling location and collection procedures

Over a seven-day period in March 2011, wastewater was collected as 24 h-composite samples from a WWTP in England. Composite sampling was performed continuously over the week (every 30 mins) and directly after inlet treatment, which included coarse screens, grit removal and fine screens. This treatment works is supplied with sewage primarily from a combined sewer infrastructure (~95 %) as well as a small proportion from separate sewers (remaining 5 %). Five pumping stations are used to deliver sewage to this WWTP (4 of which operate intermittently for 30 min every hour and one which is operated continuously). The population served by the WWTPs was 3,400,000 inhabitants and therefore represented the largest of its kind in the EU. The measured flow rate of influent wastewater through this WWTP across the week was 13,300 ± 2400 L/s and measurements were made every 15 min at the outfall channel (with an instrument error of ~8 %). On any typical dry weather day, the flow rate normally ranges from 8,000-16,000 L/s and can rise as high as 26,000 L/s during wet weather. All samples were collected in amber silanised bottles with Teflon-faced caps and frozen in a -20 ^{o}C freezer at the WWTP until collection (Fisher, UK). Samples were subsequently transported back to the laboratory in a dark and iced cool box and stored at -20 ^{o}C until analysis.

1.2.2. Chemicals and materials

Over sixty analytes were chosen for this study (Table S1). A detailed discussion on compound selection is presented in the Supplementary Material section. Among chosen analytes are:

- stimulants and their metabolites: cocaine, benzoylecgonine, norbenzoylecgonine, norcocaine, cocaethylene, anhydroecgonine methyl ester, ecgonidine, amphetamine, methamphetamine, methcathinone, BZP (benzylpiperazine), TFMPP (1-(3-trifuoromethylphenyl)piperazine),
- hallucinogens and their metabolites: MDA (3,4-methylenedioxyamphetamine), MDMA (3,4-methylenedioxymethamphetamine), MDEA (3,4-methylenedioxyethylamphetamine), MBDB (methylbenzodioxazolylbutanamine), BDB

(benzodioxazolylbutanamine), mescaline, LSD (lysergic acid diethylamide), O-H-LSD (2-oxo-3-hydroxy-LSD),

- opioids, morphine derivatives and their metabolites: heroin, 6-acetylmorphine, codeine, norcodeine, oxycodone, oxymorphone, morphine, normorphine, dihydrocodeine, buprenorphine, norbuprenorphine, methadone, EDDP (2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine), EMDP (2-ethyl-5-methyl-3,3-diphenylpyrroline), fentanyl, norfentanyl, propoxyphene, norpropoxyphene, tramadol, nortramadol,
- benzodiazepines and their metabolites: temazepam, diazepam, nordiazepam, nitrazepam, 7-aminonitrazepam, oxazepam, chlordiazepoxide,
- antidepressants and their metabolites: dosulepin, amitriptyline, nortriptyline, fluoxetine, norfluoxetine, venlafaxine,
- dissociative anesthetics and their metabolites: phencyclidine, ketamine, norketamine,
- other: methaqualone, sildenafil, ephedrine, norephedrine, caffeine, 1,7-dimethylxanthine, nicotine and continine.

Surrogate/internal standards were all purchased from LGC (UK), with the exception of caffeine-d_9 (Sigma-Aldrich, UK). All standards and internal standards were of the highest purity available (>97%). Individual stock solutions were purchased or prepared from powdered substance in either acetone or methanol at a concentration of 1 or 0.1 g L^{-1} and stored in the dark at −20 ^{o}C. LC-MS mobile phase solvents and additives were all of LC–MS quality and purchased from Sigma–Aldrich (UK) and Fisher (UK). Ultra-pure water used for pressurised liquid extraction (PLE) was taken from a Barnstead Nanopure water purification system (Thermo Fisher Scientific, UK).

1.2.3. Analytical methodology

The analytical methodology was carried out according to the validated protocol described elsewhere (Baker and Kasprzyk-Hordern 2011a-c). A brief discussion on methodology and its validation is provided in the *Supplementary Material* section (see Analytical Methodology and Tables S2-4). All samples were prepared using solid-phase extraction and PLE (for extraction of suspended solids). All analyte determinations were performed using ultra-high pressure liquid chromatography coupled with tandem mass spectrometry (using a Waters ACQUITY UPLC^{TM}-TQD instrument). Liquid chromatography separations were achieved with an ACQUITY UPLC BEH C_{18} (1.7 µm; 1 × 150 mm) column.

1.2.4. Sewage epidemiology back-calculations

Measured concentrations (ng L^{-1}) of target analytes in wastewater influent were used to back-calculate drug usage in local areas. Estimations were made for DTRs that were detected in wastewater influent and for which the necessary excretion data was available; hence back-calculations were not possible for all compounds. Estimations were based on an approach first described by Zuccato et al. (2005) and subsequently modified in this study. The modifications to the calculation represents an attempt to account for the sorption of target analytes to SPM and stability of analytes in wastewater; factors which previous authors (Zuccato, Chiabrando et al. 2005, Bones, Thomas et al. 2007, Boleda, Galceran et al. 2009, Kasprzyk-Hordern, Dinsdale et al. 2009, Postigo, de Alda et al. 2009, Karolak, Nefau et al. 2010, Terzic, Senta et al. 2010) assumed negligible due to lack of data. The following description and formulas describe the method by which estimates were calculated.

The concentration (ng L^{-1}) of a given DTR was firstly multiplied by the flow rate (L day^{-1}) of influent. This number was then corrected to account for stability and adsorption to solids, as listed in Table 1. Assuming no loss of sewage water along the pipes (none was recorded either as a planned overflow or outage during this period), this provided an estimate of the load (g

day^{-1}) of a selected DTR arriving at a selected treatment plant. The formula used to calculate daily loads is shown in Equation 1. The percentage excretion of a target DTR was then taken into account (after *relevant* forms of administration), along with the molar mass ratio between the parent drug and the DTR to provide an estimate of the load of parent drug (g day^{-1}). The load of parent drug was then divided by the number of people served by the WWTP in order to equate the load per 1000 people (mg day^{-1} 1000 people^{-1}). The detection of a DTR in wastewater may also be as a result of discharge from other irrelevant sources. In these cases the amount should be subtracted from consumption estimates. The formula to calculate mg day^{-1} 1000 people^{-1} is shown in Equation 2.

$$Load = Concentration \times Flow \times \left(\frac{100}{100 + Stability}\right) \times \left(\frac{100}{100 - Sorption}\right) \times \frac{1}{10^3}$$

Equation 1 – Load per day calculation

Where: *Concentration* corresponds to the DTR concentration (ng L^{-1}), *Flow* to the wastewater influent volume over a 24 hour period (m^3 day^{-1}), *Stability* the stability change of each compound (%) after 12 hours and *Sorption* the sorption (%) of each compound to SPM.

$$Consumption = 1000 \times Load \times \left(\frac{1}{Excretion}\right) \times \left(\frac{MW_{Par}}{MW_{DTR}}\right) \times \left(\frac{1000}{Population}\right) - OS$$

Equation 2 – mg day^{-1} 1000 people^{-1}

Where: *Load* corresponds to the amount of DTR arriving at the WWTP (g day^{-1}); *Excretion* - the percentage excretion of the DTR after relevant forms of administration; MW_{Par} - the molecular weight of the parent compound and MW_{DTR} - the molecular weight of the DTR. *OS* refers to the amount of DTR that is present in wastewater due to other sources other than the parent compound, if applicable (mg day^{-1} 1000 people^{-1}).

1.3. Results and discussion

The levels of drugs of abuse and metabolites quantified in wastewater and suspended particulate matter are summarised in Tables S5 and S6. Corresponding loads (g day^{-1}) of analytes in wastewater are listed in Table 2.

1.3.1. Drug consumption at community level (wastewater derived back-calculations)

Several DTRs were frequently quantified at sometimes relatively high concentrations in both wastewater influents and in suspended matter, as presented in Table S5 and 6. These concentrations were extrapolated to estimate loads of target analytes and consumption of parent drugs in local communities. Estimations were only possible for those DTRs that were detected in wastewater and for which excretion data was available that was derived from relevant forms of administration.

1.3.1.1. Common illicit/drugs of abuse

1.3.1.1.1. Cocaine

Back-calculations for cocaine use in local communities have been carried out in several ways in the literature. The most common method is through the use of benzoylecgonine loads, as first proposed by Zuccato et al. (2005) and subsequently followed by several other authors (Huerta-Fontela, Galceran et al. 2008, Boleda, Galceran et al. 2009, Postigo, de Alda et al. 2009, Karolak, Nefau et al. 2010, Terzic, Senta et al. 2010, van Nuijs, Mougel et al. 2011, Kinyua and Anderson 2012, Lai, Bruno et al. 2013). In contrast, Bones et al. (2007) employed the use of loads of parent compound, cocaine. Benzoylecgonine has been shown to be more

stable in wastewater compared to cocaine (Baker and Kasprzyk-Hordern 2011). Secondly, as cocaine may be present in wastewater due to direct disposal, the presence of benzoylecgonine is more indicative of human consumption. Therefore it was unsurprising that, under such circumstances, over-estimations of community consumption were observed using cocaine as a DTR in previous work (Kasprzyk-Hordern, Dinsdale et al. 2009). The use of ecgonine methyl ester as a DTR was also explored by van Nuijs et al. (2011), but the authors found no significant calculated differences to the use of benzoylecgonine in community-wide consumption estimates. However, the authors decided to retain use of benzoylecgonine as it displayed better stability in wastewater compared to ecgonine methyl ester (Baker and Kasprzyk-Hordern 2011). Uncertainties related to cocaine use back-calculation are discussed by Castiglioni et al. (Castiglioni, Bijlsma et al. 2013).

In this study, cocaine consumption estimates based on the measured loads of the metabolite, norbenzoylecgonine, are also provided, along with both benzoylecgonine and parent compound loads. Average cocaine estimates over the one week sampling period for the three DTRs are shown in Table 3. The results show that consumption estimates are significantly higher when cocaine is used as a DTR. In this case, usage of cocaine was estimated to be on average 9,793 mg day^{-1} 1000 $people^{-1}$, while using benzoylecgonine it was estimated to be 1,263 mg day^{-1} 1000 $people^{-1}$. By comparing calculated estimates using norbenzoylecgonine and benzoylecgonine as DTRs, similar results were observed (1,368 mg day^{-1} 1000 $people^{-1}$). Norbenzoylecgonine previously showed good stability in wastewater (Baker and Kasprzyk-Hordern 2011) and maybe it is a suitable DTR; however, as it is a minor metabolite (excretion = 0.95%), errors could be introduced with only slight changes in excretion values. Nonetheless, it is worth considering the use of all three metabolites as DTRs (benzoylecgonine, norbenzoylecgonine and ecgonine methyl ester), where detected above the method quantification limits, and thereby potentially removing the reliance of targeting a single analyte. Based on excretion data for cocaine after consumption (excretion of cocaine = 1.45 %, excretion of benzoylecgonine = 30.07 %) and their molar mass relation, the excreted COC/BE ratio should be ~0.05 (with a range from 0.02 to 0.27 according to Postigo et al. (Postigo, de Alda et al. 2009). In this work, the average ratio in wastewater influent was higher than expected from excretion rates, with an average ratio of 0.42±1.5. This value is consistent with the ratios determined in Belgium by van Nuijs et al. (2009) which were typically in the range 0.30 – 0.50. This seemingly higher ratio is therefore proposed to be due to higher cocaine concentrations. Predicted loads of benzoylecgonine matched up reasonably well with experimentally determined loads in the work by Kahn et al. (2011) and back-calculations using benzoylecgonine compared well with official drug statistics in several countries (van Nuijs, Castiglioni et al. 2011, van Nuijs, Castiglioni et al. In press). Several potential causes of such varied calculated cocaine concentrations have been/are proposed:

1. Direct disposal of cocaine into the sewage system (Kasprzyk-Hordern, Dinsdale et al. 2009, Postigo, de Alda et al. 2009, van Nuijs, Castiglioni et al. In press). However, as the COC/BE ratio was high in nearly every sample collected during this study and the study of 41 treatment plants by Van Nuijs et al. (2009), one would assume constant direct disposal of cocaine is unlikely.
2. An undocumented legal usage of cocaine. NHS prescription data for England (NHS 2011) has suggested only very negligible amounts are prescribed and therefore, in relation to measurements made on this scale, this is also unlikely.
3. Another potential reason could be due to the excretion of cocaine as the unchanged drug in alternative excretion routes (e.g. in sweat). Consequently, unchanged cocaine may enter the sewage system due to washing. Currently, however, to the authors knowledge there

is no data to establish whether or not significant amounts of cocaine are excreted through this route.

4. Co-administration of cocaine with ethanol may increase the amount of excreted parent drug (Khan and Nicell 2011). This is a logical suggestion, but more knowledge is required. Cocaethylene, a metabolite formed through co-administration of cocaine and ethanol, was detected in increased amounts on weekends during two, one-week monitoring studies; hence it can be suggested that co-administration of cocaine and ethanol is far increased during the weekend in relation to weekdays. In comparison, analysis of COC/BE ratios during the two one-week monitoring studies found little difference in the ratios during weekdays and the weekends.

5. Variation in the metabolic COC/BE ratio may occur before sampling given the chemical and microbial complexity of municipal sewage. At the very least, storage stability studies indicate that transformation occurs over a relatively short period for cocaine-related species (Baker and Kasprzyk-Hordern 2011, González-Mariño, Quintana et al. 2012).

The results obtained indicate that the average usage of cocaine in the area studied was estimated to be 1,263 mg day^{-1} 1000 people^{-1} (Table 3, based on benzoylecgonine loads). The results of this study are in accordance with data obtained by others (Zuccato, Chiabrando et al. 2005, Bones, Thomas et al. 2007, Huerta-Fontela, Galceran et al. 2008, Zuccato, Chiabrando et al. 2008, Boleda, Galceran et al. 2009, Kasprzyk-Hordern, Dinsdale et al. 2009, Postigo, de Alda et al. 2009, van Nuijs, Pecceu et al. 2009, Karolak, Nefau et al. 2010, Terzic, Senta et al. 2010, van Nuijs, Mougel et al. 2011). The daily results of the one week monitoring study showed that increased amounts of cocaine were consumed during the weekend. Table 2 shows the daily loads of cocaine DTRs (parent compound, benzoylecgonine, cocaethylene and norbenzoylecgonine), with an increase in the loads of all four DTRs. This increase was especially apparent for cocaethylene, when compared to benzoylecgonine, on the weekend compared to weekdays. This finding would suggest that co-administration of cocaine and ethanol is far more pronounced during the weekend as opposed to weekdays. This weekend or recreational use of cocaine is consistent with official EMCDDA reports (EMCDDA 2009), and wastewater analysis in both Belgium (van Nuijs, Mougel et al. 2011) and Croatia (Terzic, Senta et al. 2010).

1.3.1.2. Amphetamine

Determination of amphetamine consumption has widely utilised the parent compound as the DTR (Zuccato, Chiabrando et al. 2008, Kasprzyk-Hordern, Dinsdale et al. 2009, Postigo, de Alda et al. 2009, Terzic, Senta et al. 2010, van Nuijs, Mougel et al. 2011). The results of back-calculations for these studies are listed in Table 3. In this study, the average consumption was 86 mg day^{-1} 1000 people^{-1}. These results compare well with reported results in Belgium (van Nuijs, Mougel et al. 2011), Croatia (Terzic, Senta et al. 2010), Italy and England (London) (Zuccato, Chiabrando et al. 2008).

The contribution of legal consumption of amphetamine in sewage, including the occurrence of their associated excreted metabolites of selegiline and methamphetamine (refer to *Supplementary Material*), makes the estimation of illicit amphetamine usage challenging. In England in 2010, 14.1 kg of selegiline and 23.8 kg of amphetamine were prescribed, with a dose of selegiline excreted mainly as methamphetamine and amphetamine (excretion rates have not been reported for selegiline to the author's knowledge). In relation to consumption estimates for England, prescribed values are negligible; accounting for approximately 1 mg day^{-1} 1000 people^{-1} (assuming a dose of selegiline is excreted as 50 % amphetamine).

Amphetamine is a recreational drug that is often associated with 'nightclub' culture (EMCDDA 2009). This was seemingly confirmed through daily monitoring of amphetamine levels in Croatia by Terzic et al. (2010), with higher amphetamine loads reported during the weekend in comparison to weekdays. However, no increase in amphetamine use was observed here during the weekend. Reasons for this could be that usage of amphetamine follows a different pattern in England and legal usage throughout the week is significant. More importantly, it must be remembered that the presence of amphetamine in wastewater was not confirmed, hence an unknown compound could have potentially been quantified with amphetamine and resulted in an overestimation of values (see papers by Baker and Kasprzyk-Hordern for further discussion (Kasprzyk-Hordern, Kondakal et al. 2010, Baker and Kasprzyk-Hordern 2011, Baker and Kasprzyk-Hordern 2011)). For this reason, further investigation into the analytical problems surrounding amphetamine analysis is required. Chiral analysis of enantiomers of amphetamine should be also undertaken to help with differentiating between direct disposal, consumption, and legal and illicit use (Kasprzyk-Hordern and Baker 2012).

1.3.1.3. Methamphetamine

The average consumption of methamphetamine was determined to be 17 mg day^{-1} 1000 $people^{-1}$. The results of this study are higher from those of Postigo et al. (2009) in which methamphetamine was detected in only 14 % of samples, with an average consumption of 1.5 mg day^{-1} 1000 $people^{-1}$ aged 15-34 and the results of van Nuijs et al. (2011) in which an average consumption of 2 mg day^{-1} 1000 $people^{-1}$ was determined.

Consumption estimates for methamphetamine are consistent with official Home Office data which suggests that abuse of methamphetamine is low with only 0.1 % of those aged 16 – 59 years having taken the drug in the last year in England and Wales; with usage of methamphetamine also typically low for most European countries (EMCDDA 2009). The weekly monitoring campaign indicated an increase in weekend use (Table 3).

1.3.1.4. MDMA

The mean consumption of MDMA was 148 mg day^{-1} 1000 $people^{-1}$, see Table 3. The average consumption determined in this study is higher than the reports of 13 and 3.6 mg day^{-1} 1000 $people^{-1}$ in Belgium and Croatia (Terzic, Senta et al. 2010, van Nuijs, Mougel et al. 2011), while the results of the study are generally consistent with the 200 mg day^{-1} 1000 $people^{-1}$ reported in Spain (Huerta-Fontela, Galceran et al. 2008).

Table 3 presents the determined consumption in over the week long monitoring campaign. The results show that levels of MDMA increase substantially during the weekend, which is consistent with reports of MDMA use as a 'club' drug (EMCDDA 2009). The increase in levels at the weekend are also similar to the results of wastewater analysis reported in Belgium (van Nuijs, Mougel et al. 2011) and Croatia (Terzic, Senta et al. 2010).

1.3.1.5. Heroin

In previously reported studies, estimates for heroin consumption have employed either morphine (Zuccato, Chiabrando et al. 2008, Boleda, Galceran et al. 2009, Postigo, de Alda et al. 2009, Terzic, Senta et al. 2010) or 6-acetylmorphine (van Nuijs, Mougel et al. 2011) as DTRs. However in the authors' opinion, neither DTR is suitable to estimate heroin usage.

Morphine has several legal sources, which includes morphine itself, codeine, ethylmorphine, nicomorphine, pholcodine (Baselt 2008). In previously published literature, authors have subtracted estimated loads of morphine resulting from legal use of morphine itself, and then used the remaining amount of morphine to estimate heroin consumption, as first reported by

Zucatto et al. (2008). However, in England, the amount of morphine and codeine distributed is significant. In England in 2010, 3993 kg of morphine and 37117 kg of codeine were distributed (NHS 2011). Assuming a dose of morphine is excreted as 77 % parent compound and a dose of codeine is excreted as 6.0 % morphine (see Supplementary Material) this results in a total yearly amount of morphine excreted (3075 kg + 2227 kg) of 5301 kg, or 442 kg per month (assuming of course that all medication is consumed rather than directly disposed and that an equal amount of medication is used in each month throughout the year). In England and Wales in 2010, a reported 0.04 % of people aged 16-59 used heroin in the last month (Home Office 2011). Thus, applying this usage statistic to the population of England aged 16-59 (30,721,241 people aged 16-59, (ONS 2010)), gives a total 12,288 users a month (assuming one dose per person a month). A typical daily dose of heroin at street purity is 100 mg (EMCDDA 2010) or 30 mg (INCB 2008, UNODC 2008). Hence, if 12,288 users consume the reported average daily dose (using a midpoint of 65 mg), this results in a monthly heroin consumption of 0.80 kg. Taking into account that a heroin dose is excreted as 55 % morphine gives a total of 0.44 kg of morphine a month related to heroin usage. Comparing this figure of 0.44 kg illicit morphine to that of 442 kg legal morphine, shows that only 0.01 % of morphine in wastewater is related to illegal usage. This is of course an approximate value based on several mentioned assumptions; nevertheless it provides evidence for that fact that morphine is a completely unsuitable DTR - in England at least. This finding is likely to be true for several other countries where morphine and codeine usage is relatively high in relation to heroin usage. Furthermore, whilst the measured component sorbed to solids was 0.9 % here, previous works have shown that transformation or degradation of morphine is likely in semi-solid suspensions and which may therefore result in an under-estimation of morphine concentration after a very short residence time (Barron, Havel et al. 2009). In this reported work, the liquid-phase concentration diminished rapidly within 24 h (<10 % after 12 h) and the measured sorbed component also remained low (as here) leading to a mass imbalance.

The alternative DTR to monitor heroin is the minor metabolite 6-acetylmorphine. To date, only van Nuijs et al. (2011) have based back-calculations on this compound. A major advantage of this DTR is that there are no significant additional sources as with morphine. On the other hand, 6-acetylmorphine is a minor metabolite of heroin (Khan and Nicell 2011), hence analytical detection limits need to be low and correction factors for back-calculations are high, meaning high uncertainties could be introduced. However the main problem with the usage of 6-acetylmorphine at present is the lack of relevant excretion data. In the study by van Nuijs et al. (2011) an excretion rate of 1.3 % was used. This value of 1.3 % is based on data generated by irrelevant prolonged infusion (Elliott, Parker et al. 1971); hence the excretion rate is likely to be different for relevant forms of administration such as chasing (excretion of heroin is covered in more detail in Supplementary Material). For this reason, until excretion data is published for relevant forms of administration, in the authors' opinion, back-calculations are not appropriate. As 6-acetylmorphine is relatively unique to heroin, it could be nevertheless a suitable target residue to monitor WWTP loads.

1.3.1.6. Methadone

In England, methadone is administered to patients under supervised conditions for at least three months and until they are deemed 'stable' (NHS 2009, NHS 2010). The controlled nature under which methadone is administered makes it a suitable compound to monitor in the environment as direct disposal or administration by other means is unlikely due to the supervision of medical staff during administration in the UK. Furthermore, prescription records for methadone are readily available.

During the monitoring study, three excreted products for methadone were analysed (parent compound, EDDP and EMDP). As direct disposal is unlikely in the case of methadone, parent compound itself is a suitable DTR in addition to the metabolites. Back-calculations using the three DTRs are listed in Table 3. Average consumption of methadone using parent compound as the DTR was determined to be 84 mg day^{-1} 1000 people^{-1}, which is slightly lower than that determined using EDDP as the DTR of 113 mg day^{-1} 1000 people^{-1}. NHS prescription data for methadone in England in 2010 reported that 1856 kg of the free base was prescribed; the equivalent of 97 mg day^{-1} 1000 people^{-1}.

The average consumption estimate of this study (113 mg day^{-1} 1000 people^{-1}) is marginally lower than the average 138 mg day^{-1} 1000 people^{-1} estimated in Belgium (van Nuijs, Mougel et al. 2011) and 148 mg day^{-1} 1000 people^{-1} estimated in Croatia (Terzic, Senta et al. 2010). In both of the previous studies EDDP was used as the DTR; back-calculations using parent compound as the DTR were not reported.

Mass loads during daily, one week monitoring studies presented no pattern of usage, with loads of EDDP and methadone relatively consistent throughout the week, see Table 2. This is a logical observation since, as previously mentioned, methadone is administered under the supervision of medical staff.

1.3.1.7. TFMPP and BZP

Consumption estimates for TFMPP and BZP are not possible due to the lack of human elimination data for these compounds, see Supplementary Material. Nevertheless, it is possible to monitor the loads of these compounds at a WWTP to assess whether or not any patterns are visible. Mass loads during one week monitoring studies indicated low use of both TFMPP and BZP. This finding is consistent with reports of TFMPP use on the ‘club’ or ‘rave’ scenes (U.S. DEA 2003).

1.3.1.8. Ketamine

Ketamine use in England and Wales has doubled over the last four years (Home Office 2011). Back-calculations for ketamine are not possible for two reasons. Firstly there are no data, to the author’s knowledge, relating to the percentage of elimination of each metabolite after a dose of ketamine is consumed through insufflation; the primary route of administration (Wills 2005). Ketamine may also be consumed orally (Moore, Sklerov et al. 2001, Kim, Lee et al. 2008, Parkin, Turfus et al. 2008) and intravenously (Wieber, Gugler et al. 1975, Adamowicz and Kala 2005). Secondly ketamine is used as a veterinary drug, for which there is no distribution data, hence veterinary use cannot be distinguished from human use. Although back-calculations cannot be reliably attempted it is possible to monitor loads of ketamine over an extended period.

Loads of ketamine during daily, one week monitoring studies are presented in Table 2. As ketamine is regarded as a ‘club’ drug (Sproule 2006) it was expected to see an increase of loads due to human usage at the weekend; this was not observed.

1.3.2. Prescription/over-the-counter drugs of abuse

The method discussed here can be applied to almost any other chemical with an understood fate and route of disposal. Therefore the consumption of prescription/over-the-counter drugs was also verified using the above approach. Obtained values from wastewater analysis were compared with prescription data by the NHS (NHS 2011), and where possible with estimated over-the-counter sales. NHS prescription data covers prescriptions dispensed in the community, i.e. community pharmacists, dispensing doctors, and items personally administrated by doctors and also dentists and hospital doctors. The data does not include

items dispensed in hospitals or on private medications. A comparison between wastewater estimates in this current study and NHS data is presented in Table 4.

1.3.2.1. Codeine

In England in 2010, 31925 kg of codeine free base were prescribed (NHS 2011), in addition to an estimated 5192 kg over-the-counter sales (see Supplementary Material). This distribution data corresponds to an estimated 1946 mg day^{-1} 1000 people^{-1}. During wastewater analysis, both codeine and norcodeine were determined. Consumption estimates based on parent compound as a DTR were on average 565 mg/day/1000 people, and based on norcodeine as a DTR estimates were on average 225 mg day^{-1} 1000 people^{-1}, see Table 4. Therefore, wastewater consumption estimates were someway short of the estimate based on NHS data. There are many potential reasons for underestimation between NHS data and wastewater data. For instance, the excretion data used to carry out back-calculations may not have been representative of the local population resulting in under-reporting or not all prescribed codeine was consumed/disposed of. Similarly, as codeine also metabolises to morphine, similar transformation effects may occur as discussed above.

1.3.2.2. Tramadol

Results based on wastewater analysis with NHS prescription data compared well in this case. Based on NHS data, consumption of tramadol in 2010 in England was 1654 mg day^{-1} 1000 people^{-1}. Wastewater analysis using tramadol as the DTR was on average 1067 mg day^{-1} 1000 people^{-1}, while using the metabolite nortramadol as the DTR provided similar estimate of 948 mg day^{-1} 1000 people^{-1}, see Table 4. Combined with this, sorption of tramadol to solids is generally expected to be low and this was confirmed again here (Barron, Havel et al. 2009). Relative variance using the parent compound is likely to be low in comparison to some other species studied here given its % excretion at 31.9 %.

1.3.2.3. Dihydrocodeine and oxycodone

Results based on wastewater analysis compared to NHS data for both dihydrocodeine and oxycodone were in good agreement, see Table 4. The consumption estimate for dihydrocodeine based on NHS data was 225 mg day^{-1} 1000 people^{-1} and the estimate determined through wastewater analysis was, on average, 244 mg day^{-1} 1000 people^{-1} in this study.

Based on NHS data, consumption of oxycodone was approximately 54 mg day^{-1} 1000 people^{-1}. This is consistent with the wastewater figure of 20 mg day^{-1} 1000 people^{-1} estimated when using parent compound as the DTR. The estimate when using oxymorphone as the DTR was slightly higher at 29 mg day^{-1} 1000 people^{-1}. Results obtained when using oxycodone and oxymorphone as DTRs is shown in Table 4.

1.3.2.4. Propoxyphene

Back-calculations for propoxyphene were based solely on the metabolite norpropoxyphene, as parent compound was rarely detected in wastewater influent samples (please see the Supplementary Material Section for method detection/quantification limits). Based on norpropoxyphene as the DTR, consumption of propoxyphene was on average 249 mg day^{-1} 1000 people^{-1}. This is roughly 5 times higher than that estimated based on NHS data of 47 mg day^{-1} 1000 people^{-1}. Over-estimation of drug usage may be a result of several factors such as: distribution of drug that has not been recorded in NHS data, different consumption patterns in local areas and excretion rates used in back-calculations may not have been representative of the local population.

1.3.2.5. Temazepam and diazepam

Back-calculations of diazepam were estimated using oxazepam as a DTR. Back calculations using the parent compound were not possible as diazepam was not detected in analysed samples (please see the Supplementary Material Section for method detection/quantification limits) and the percentage excretion of nordiazepam has not been accurately reported and so cannot be used. As discussed in the Supplementary Material, however, oxazepam is also a drug itself and is almost entirely excreted as the parent (or the conjugate) with 94.5 kg of the free base prescribed in 2010 (the equivalent of 1.81 mg day^{-1} 1000 $people^{-1}$). Oxazepam is also a metabolite of temazepam, although it is a relatively minor metabolite and hence will be considered negligible for back-calculation purposes. Back-calculations of diazepam using oxazepam as the DTR, minus prescribed oxazepam, resulted in an average estimate of 28 mg day^{-1} 1000 $people^{-1}$ which is in good agreement with the estimate of 37 mg day^{-1} 1000 $people^{-1}$ based on NHS prescription data.

Temazepam is predominately excreted as parent compound and conjugated parent compound, hence temazepam itself was utilised as the DTR. Back calculations for temazepam resulted in an average consumption estimate of 75 mg day^{-1} 1000 $people^{-1}$, which compares relatively well with the estimate of 54 mg day^{-1} 1000 $people^{-1}$ based on NHS prescription data.

1.3.2.6. Dosulepin

Consumption estimates using the parent compound as a DTR in wastewater resulted in an estimate of 111 mg day^{-1} 1000 $people^{-1}$, which correlates with the estimate based on NHS data of 191 mg day^{-1} 1000 $people^{-1}$ (Table 4).

1.3.2.7. Amitriptyline

Based on NHS prescription data on average 419 mg day^{-1} 1000 $people^{-1}$ of amitriptyline is consumed per year. The value of 101 mg day^{-1} 1000 $people^{-1}$ estimated when nortriptyline was used as a DTR is lower than the NHS estimate. However when the parent compound was used as the DTR, a seemingly inflated figure of 2154 mg day^{-1} 1000 $people^{-1}$ was estimated. Over-estimation based on using the parent compound as a DTR is likely a result of the very low excretion factor (2 %) used in the back-calculation. Hence, as the excretion factor is low, if the excretion percentage in reality deviates significantly from this then it will have a major impact of the result. Furthermore, it should be noted that sorption of amitriptyline, fluoxetine and dosulepin-related compounds are expected to be high given their relative logP/logD and this was apparent here also. In particular, nortriptyline and amitriptyline have been shown to sorb heavily to sewage sludges at 600-1049 L/kg respectively (Barron, Havel et al. 2009). Some sorption in sewage prior to sampling is also likely to occur and could account for the variable estimates here.

1.3.2.8. Fluoxetine

Consumption estimates for fluoxetine were relatively similar at all WWTPs when using both parent compound and norfluoxetine as DTRs, see Table 4. Based on NHS prescription data a consumption estimate of 226 mg day^{-1} 1000 $people^{-1}$ people is derived, which compares well with the estimate of 98 mg day^{-1} 1000 $people^{-1}$ people using parent compound as a DTR and 54 mg day^{-1} 1000 $people^{-1}$ using norfluoxetine as a DTR. Again, lower estimates could arise from sorption to suspended solids prior to sampling. It is clear, that further work is required on these compounds if the back-calculation approach is to be extended to over-the-counter drugs.

1.3.2.9. Venlafaxine

Consumption estimates for venlafaxine based on using the parent compound as a DTR showed a large over estimation in comparison to NHS data. NHS prescription data shows that approximately 417 mg day^{-1} 1000 $people^{-1}$ is consumed, which is far lower than the 1276 mg day^{-1} 1000 $people^{-1}$ estimated through using parent compound as the DTR. Sorption of venlafaxine was low here, and consistent with other studies with sludge interaction (Hörsing, Ledin et al. 2011). However, data from stability during storage (up to 20 % reduction after 12 h) indicate that some losses are likely before the sampling point (Baker and Kasprzyk-Hordern 2011). A more appropriate DTR is likely to be the main metabolite O-desmethylvenlafaxine.

1.3.2.10. Other compounds

Caffeine loads remained stable during the monitoring week. Consumption estimated for caffeine based on using the parent compound as a DTR were significantly overestimated (742 g day^{-1} 1000 $people^{-1}$) when compared with consumption estimated obtained for DTR 1,7-dimethylxantine (190 g day^{-1} 1000 $people^{-1}$) (Table 3). Nicotine loads remained, as expected, constant throughout sampling week and denoted on average 0.91 g day^{-1} (Table 2). Nicotine consumption could not be estimated as its metabolic DTR could not be quantified in wastewater. Sildenafil's daily mass loads were observed to increase during weekends possibly due to its abuse potential; however its consumption could not be estimated due to lack of metabolic DTR.

Caffeine, nicotine as well as prescription pharmaceuticals such as antidepressants could be used to estimate population size served by studied wastewater treatment plant. Such an investigation will be subject to further research.

2. Conclusions and future outlook

The above results show the usefulness of wastewater analysis in order to provide estimates of local community drug consumption. It is noticeable that where target compounds could be compared to NHS prescription statistics, good comparisons were apparent between the two sets of data. These compounds include oxycodone, dihydrocodeine, methadone, tramadol, temazepam, diazepam. Whereas, discrepancies were observed for propoxyphene, codeine, dosulepin and venlafaxine (over-estimations in each case except codeine). Potential reasons for discrepancies were discussed above for each compound, but in general, these factors include: sales of drugs sold without prescription and not included within NHS data, abuse of a drug with the compound trafficked through illegal sources, different consumption patterns in different areas, direct disposal leading to over estimations when using parent compound as the DTR and excretion factors not being representative of the local community. It is noticeable that using a metabolite (and not a parent drug) as a biomarker leads to higher certainty of obtained estimates. With regards to illicit drugs, consistent and logical results were reported. Monitoring of these compounds over a one week period highlighted the expected recreational use of many of these drugs (e.g. cocaine and MDMA) and the more consistent use of others (e.g. methadone).

The sewage epidemiology approach has a number of advantages in comparison to current methods of estimation, such as population surveys, crime statistics and hospital admissions. Wastewater analysis provides near-real time data, with sample collection, analysis and data reporting achieved in around 24 hours (depending on the time of sample collection). This would allow relevant authorities to rapidly identify emerging hotspots of drug abuse and also assess the effectiveness of counter measure tactics. The analysis of wastewater may provide a more reliable estimation of drug usage; as data is generated from a direct source rather than

indirect sources such as population surveys in which participants may (for example) be untruthful about their drug habits.

Knowledge of the excretion of a DTR after consumption plays a crucial role in back-calculations of drug consumption. However the majority of published data has many flaws for utilisation in sewage epidemiology back-calculations. For instance, the majority of data is rather old (typically early 1980's), and is based on a limited number of subjects. Furthermore, the administration method in some cases is not relevant to the manner in which the drug is consumed nowadays and the dosage size administered is often far smaller. Typically, large deviations are reported in the excretion percentages of a DTR, such as MDMA, which has a reported excretion ranging from 5.9 to 47.7 % (Khan and Nicell 2011). To improve knowledge of the excretion of a DTR, a comprehensive literature search should be carried out. This is a difficult process, given the lack of publications and the age of the publications making retrieval of information problematic. In order to unambiguously define excretion of selected drugs of abuse, new more comprehensive pharmacokinetic studies should be carried out that resolve issues surroundings number of subjects, administration, dosage size and with analysis of urine, faeces and sweat of subjects. Pharmacokinetic studies, however, are not a straightforward affair; hence a significant amount of time and funding will be required to accomplish this goal.

Back-calculations are also subject to two other important parameters; the number of inhabitants served by the WWTP and the flow rate. The number of inhabitants served by a WWTP is constantly changing due to factors such as commuting and holidays. Typically, local population census information or WWTP design capacity is used to estimate population. An alternative method could be to determine biological oxygen demand (BOD), chemical oxygen demand (COD), total phosphorous (P) and nitrogen (N) in wastewater. These measurements may enable the indication of population (Zessner and Lindtner 2005, Garnier, Laroche et al. 2006), with recent application for the first time with regards to drugs of abuse by van Nuijs and co-workers (2011). Although BOD, COD, N and P may help indicate population, they are not ideal, as measurements require another analytical method. Ideally, a human indicator present in samples that may be analysed along with the targeted drugs of abuse would allow significant efficiencies as one method would be required for analysis. Among such compounds may be: creatinine, metabolites of caffeine, nicotine or prescription medications. With regards to the flow rate, over or under-estimation can have a significant impact on calculated loads. To minimise the error from this variable, relevant WWTP personnel should be contacted. It is likely that error with regards to flow rate measurements will be 'low' in modern WWTPs (Zuccato, Chiabrando et al. 2008).

Estimation of uncertainty for this study is a subject covered in the sister paper entitled 'Illicit and pharmaceutical drug consumption estimated via wastewater analysis. Part B: Accounting for the multiple sources of uncertainty' by H E Jones, M Hickman, A E Ades, N J Welton, D Baker and B Kasprzyk-Hordern.

Wastewater analysis for drug usage estimation is a promising tool. However, this methodology will never be a stand-alone approach due to inherit limitations. Estimations through wastewater analysis cannot provide data with regards to the individuals taking the drugs; for example sex, age and ethnicity. Neither can data be provided on the dose, frequency or method of administration (although the method of administration may be determined for some compounds in which differentiating metabolites can be identified, e.g. cocaine snorting and smoking). In reality, it is likely that wastewater estimations will be complimentary to classical socio-epidemical studies, with wastewater analysis allowing authorities the important capacity to generate rapid drug estimates when required.

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Table 1 – Overview of parameters used in the sewage epidemiology calculations for each compound

Compound	DTR	Stability (%)[a]	Sorption to SPM (%)[b]	% of dose excreted as DTR[c]	Molar ratio parent/DTR
Stimulants					
Cocaine	Cocaine	-7.7	1.4	1.53	1.00
	Benzoylecgonine	5.5	0.4	30.07	1.05
	Norbenzoylecgonine	3.5	0.6	0.95	1.10
	Norcocaine	-9.9	-	0.037	1.05
(cocaine + ethanol)	Cocaethylene	-6.8	1.3	unknown	0.96
(crack cocaine)	Anhydroecg. M. E.	19.8	-	0.19	1.67
	Ecgonidine	30.8	-	2	1.98
Amphetamine	Amphetamine	46.8	0.5	30	1.00
Methamphetamine	Methamphetamine	8.1	0.6	43	1.00
Methcathinone	Methcathinone	-56.5	-	5.5	1.00
BZP	BZP	55.6	-	6.7 (rat)	1.00
TFMPP	TFMPP	23.5	-	0.7 (rat)	1.00
Hallucinogens					
MDA	MDA	3.4	-	high'	1.00
MDMA	MDMA	1.4	1.1	20.3	1.00
MDEA	MDEA	-1.5	-	19	1.00
MBDB	MBDB	-8.6	-	unknown	1.00
	BDB	-20.5	-	unknown	1.07
Mescaline	Mescaline	-7.1	-	57.5	1.00
LSD	LSD	-3.5	-	31.3 (monkey)	1.00
	O-H-LSD	-4.7	-	unknown	0.00
Opioids and morphine derivatives					
Heroin	Heroin	-79.4	-	0.025	1.00
	Morphine	48.9	0.9	55.0	1.29
	6-acetylmorphine	-12.0	-	0.50	1.13
Codeine	Codeine	12.4	1.0	63.8	1.00
	Norcodeine	4.5	2.3	5.1	1.05
Oxycodone	Oxycodone	9.6	-	8.9	1.00
	Oxymorphone	31.0	-	10.7	1.05
Morphine	Normorphine	4.3	1.2	5	1.05
Dihydrocodeine	Dihydrocodeine	-6.0	1.0	54.0	1.00
Buprenorphine	Buprenorphine	-5.9	-	1.02	1.00
	Norbuprenorphine	-3.7	-	9.65	1.13
Methadone	Methadone	-6.7	7.1	27.8	1.00
	EDDP	-12.8	8.1	24.6	1.06
	EMDP	-17.7	-	1	1.12
Fentanyl	Fentanyl	-8.3	-	3.2 (intravenous)	1.00
	Norfentanyl	-13.5	-	40.5 (intravenous)	1.45
Propoxyphene	Propoxyphene	-1.8	2.0	1.3	1.00
	Norpropoxyphene	64.0	3.8	15.4	1.04
Tramadol	Tramadol	-11.0	1.0	31.9	1.00
	Nortramadol	-44.2	1.6	18.7	1.06

Benzodiazepines					
Temazepam	Temazepam	19.4	-	74.5	1.00
Diazepam	Diazepam	-3.0	-	Trace	1.00
	Nordiazepam	15.6	-	Approx. 7	1.05
	Oxazepam	2.4	5.4	33	0.99
Nitrazepam	Nitrazepam	-61.9	-	1.2	1.00
	7-aminonitrazepam	29.8	-	37.2	1.12
Chlordiazepoxide	Chlordiazepoxide	-14.4	-	6.9	1.00
Antidepressants					
Dosulepin	Dosulepin	-7.4	16.5	11.3	1.00
Amitriptyline	Amitriptyline	10.1	10.7	2	1.00
	Nortriptyline	-7.8	12.5	3	1.05
Fluoxetine	Fluoxetine	8.2	50.8	11	1.00
	Norfluoxetine	1.9	61.5	7	1.05
Venlafaxine	Venlafaxine	-20.5	0.4	5	1.00
Dissociative anaesthetics					
Phencyclidine	Phencyclidine	-3.2	-	10	1.00
Ketamine	Ketamine	-0.8	0.6	2.3 (intravenous)	1.00
	Norketamine	-2.7	0.4	1.6 (intravenous)	1.06
Other					
Methaqualone	Methaqualone	-2.7	-	0.2	1.00
Sildenafil	Sildenafil	11.5	10.3	0	1.00
Ephedrine	Ephedrine	-40.4	0.3	NA	NA
Norephedrine	Norephedrine	-65.1	-	NA	NA
Caffeine	Caffeine	8.4	-	1	1.00
1,7-dimethylxanthine	1,7-dimethylxanthine	-15.3	-	4	1.08
Nicotine	Nicotine	3.8	-	NA	NA
Cotinine	Cotinine	56.5	-	NA	NA

[a] Stability change in raw wastewater at 19 °C after 12 hours. See paper by (Baker and Kasprzyk-Hordern 2011a) for further information regarding stability studies

[b] Average sorption to SPM in collected wastewater samples. See paper by (Baker and Kasprzyk-Hordern 2011b) for further information regarding SPM analysis

[c] For further information regarding the excretion of each compound refer to *Supplementary Material*. Unless stated otherwise excretion data is derived from human studies with a relevant form of administration

Table 2 – Average load (g day^{-1}) of target analytes in sample collected over a one week period, calculated using Eq. (1).

Compound	DTR loads (g day^{-1} ± standard deviation) (n = 2)						
	10th March Thursday	11th March Friday	12th March Saturday	14th March Monday	15th March Tuesday	16th March Wednesday	17th March Thursday
Stimulants							
Cocaine	516 ± 2.1	510 ± 4.9	567 ± 0.3	670 ± 2.5	396 ± 6.6	450 ± 15	456 ± 9.7
Benzoylecgonine	1213 ± 25	1182 ± 36	1310 ± 40	1721 ± 44	1084 ± 32	1108 ± 31	997 ± 10
Norbenzoylecgonine	32.9 ± 0.1	38.5 ± 1.1	43.8 ± 0.1	61.5 ± 1.0	38.8 ± 0.6	35.1 ± 0.9	30.8 ± 1.4
Norcocaine	- -	- -	- -	- -	- -	- -	- -
Cocaethylene	21.7 ± 0.1	22.3 ± 0.3	30.2 ± 0.3	57.0 ± 1.3	24.7 ± 0.7	18.8 ± 0.5	18.5 ± 0.6
Anhydroecgonine methyl ester	- -	- -	- -	- -	- -	- -	- -
Ecgonidine	- -	- -	- -	- -	- -	- -	- -
Amphetamine	108 ± 19	101 ± 2.0	71.9 ± 0.4	104 ± 3.9	61.2 ± 1.7	79.3 ± 0.6	87.1 ± 2.3
Methamphetamine	25.2 ± 1.9	22.9 ± 0.0	20.7 ± 0.5	43.5 ± 1.4	21.2 ± 0.4	21.9 ± 0.7	19.4 ± 1.1
Methcathinone	- -	- -	- -	- -	- -	- -	- -
BZP	- -	- -	- -	- -	- -	- -	- -
TFMPP	- -	- -	1.1 ± 0.0	2.3 ± 0.3	- -	1.9 ± 0.1	- -
Hallucinogens							
MDA	- -	- -	- -	20.0 ± 0.9	- -	- -	- -
MDMA	55.2 ± 2.2	48.4 ± 0.9	62.6 ± 2.2	270 ± 8.7	107 ± 3.7	112 ± 3.0	59.1 ± 0.7
MDEA	- -	- -	- -	- -	- -	- -	- -
MBDB	- -	- -	- -	- -	- -	- -	- -
BDB	- -	- -	- -	- -	- -	- -	- -
Mescaline	- -	- -	- -	- -	- -	- -	- -
LSD	- -	- -	- -	- -	- -	- -	- -
O-H-LSD	- -	- -	- -	- -	- -	- -	- -
Opiods and morphine derivatives							
Heroin	- -	- -	- -	- -	- -	- -	- -
6-acetylmorphine	7.3 ± 0.0	7.0 ± 0.3	19.5 ± 0.4	9.4 ± 0.4	4.0 ± 0.3	4.5 ± 0.0	15.4 ± 1.3
Codeine	1199 ± 20	1220 ± 1.2	1346 ± 13	1159 ± 13	1239 ± 55	1270 ± 2.0	1129 ± 16
Norcodeine	35.3 ± 1.9	39.9 ± 1.9	38.6 ± 3.4	37.3 ± 1.8	35.3 ± 1.9	36.7 ± 2.7	37.7 ± 1.4
Oxycodone	5.4 ± 0.3	6.2 ± 1.1	5.8 ± 0.9	6.1 ± 0.5	- -	- -	- -
Oxymorphone	- -	10.7 ± 0.5	9.8 ± 0.4	9.6 ± 0.3	- -	10.1 ± 1.7	9.5 ± 1.1

Morphine	275	±	2.6	277	±	16.2	315	±	7.8	269	±	14	284	±	15	267	±	16	290	±	26
Normorphine	67.4	±	2.1	70.1	±	6.7	74	±	6.2	68.3	±	5.5	77.8	±	6.3	68.9	±	2.0	57.5	±	17
Dihydrocodeine	457	±	2.9	450	±	2.5	479	±	2.9	436	±	1.5	429	±	1.1	482	±	14.2	410	±	5.5
Buprenorphine	-		-	-		-	-		-	-		-	-		-	-		-	-		-
Norbuprenorphine	-		-	-		-	-		-	-		-	-		-	-		-	-		-
Methadone	72.3	±	1.0	76.1	±	0.1	81.4	±	0.6	76.9	±	1.4	70.0	±	0.7	77.2	±	1.1	71.7	±	1.2
EDDP	112	±	5.9	109	±	1.8	116	±	4.0	108	±	2.3	103	±	0.1	126	±	1.1	111	±	8.4
EMDP	-		-	-		-	-		-	-		-	-		-	-		-	-		-
Fentanyl	-		-	-		-	-		-	-		-	-		-	-		-	-		-
Norfentanyl	-		-	-		-	-		-	-		-	-		-	-		-	-		-
Propoxyphene	-		-	-		-	-		-	17.2	±	0.1	-		-	-		-	-		-
Norpropoxyphene	116	±	6.5	123	±	2.1	129	±	12	117	±	13	135	±	4.1	134	±	5.2	123	±	13
Tramadol	1134	±	17	1079	±	14	1037	±	16	976	±	21	1080	±	71	1100	±	17	962	±	50
Nortramadol	491	±	95	485	±	64	487	±	44	551	±	53	517	±	13	542	±	57	560	±	92
Benzodiazepines																						
Temazepam	203	±	14	206	±	1.8	183	±	12	205	±	24	171	±	7.8	199	±	15	162	±	22
Diazepam	-		-	-		-	-		-	-		-	-		-	-		-	-		-
Nordiazepam	15.1	±	3.5	16.6	±	6.4	15.2	±	3.7	12.1	±	3.8	18.3	±	6.8	16.8	±	6.2	20.0	±	12
Nitrazepam	-		-	-		-	-		-	-		-	-		-	-		-	-		-
7-aminonitrazepam	-		-	-		-	-		-	-		-	-		-	-		-	-		-
Oxazepam	32.8	±	1.0	31.5	±	2.3	31.8	±	1.9	29.9	±	1.3	31.1	±	0.3	33.6	±	0.7	26.8	±	2.0
Chlordiazepoxide	-		-	-		-	-		-	-		-	-		-	-		-	-		-
Antidepressants																						
Dosulepin	32.5	±	1.1	43.5	±	5.3	42.3	±	3.9	43.1	±	3.2	43.1	±	6.6	49.0	±	3.1	44.6	±	8.3
Amitriptyline	132	±	4.7	159	±	22	153	±	29	126	±	12	153	±	33	167	±	13	135	±	30
Nortriptyline	12.3	±	1.1	10.8	±	2.1	9.3	±	2.0	7.4	±	1.7	8.5	±	2.7	11.3	±	1.7	8.7	±	2.7
Fluoxetine	33.1	±	1.7	38.8	±	3.7	39.3	±	1.1	30.4	±	0.3	41.7	±	4.8	42.3	±	1.4	30.8	±	3.5
Norfluoxetine	11.7	±	0.1	10.9	±	3.3	9.8	±	1.8	11.1	±	4.6	15.6	±	2.6	17.0	±	0.8	9.9	±	4.4
Venlafaxine	241	±	7.7	237	±	4.0	200	±	2.6	178	±	1.0	179	±	0.3	241	±	4.9	242	±	0.4
Dissociative anaesthetics																						
Phencyclidine	-		-	-		-	-		-	-		-	-		-	-		-	-		-
Ketamine	176	±	4.3	193	±	1.4	245	±	2.2	280	±	4.2	262	±	2.4	327	±	1.4	179	±	1.2
Norketamine	31.1	±	0.8	48.3	±	0.5	66.2	±	0.7	103	±	3.1	47.7	±	0.8	52.9	±	0.5	42.5	±	0.1

Other																			
Methaqualone	-		-	-		-	-		-	-		-	-		-	-		-	-
Sildenafil	9.9	±	0.3	12.9	±	1.3	12.0	±	1.4	15.0	±	1.0	12.9	±	2.3	14.0	±	1.7	12.7	±	1.1
Ephedrine	1766	±	9.6	1890	±	91	1743	±	23	1577	±	5.0	1884	±	39	1739	±	26	1582	±	44
Norephedrine	-		-	-		-	-		-	-		-	-		-	-		-	-		-
Caffeine	27075	±	934	26420	±	380	24876	±	279	22934	±	483	22082	±	258	26929	±	105	26200	±	628
1,7-dimethylxanthine	26026	±	357	25737	±	106	22747	±	53	21992	±	201	21633	±	92	25544	±	882	24966	±	1187
Nicotine	8731	±	31.2	9061	±	122	9402	±	391	10936	±	142	8094	±	117	9392	±	191	8132	±	111
Continine	-		-	-		-	-		-	-		-	-		-	-		-	-		-

Table 3 – Wastewater derived drug consumption estimates, calculated using Eq. (2).

Compound	DTR	Loads (mg day^{-1} 1000 people^{-1} ± standard deviation) (n = 2)						
		10th March Thursday	11th March Friday	12th March Saturday	14th March Monday	15th March Tuesday	16th March Wednesday	17th March Thursday
Stimulants								
Cocaine	Cocaine	9922 ± 41	9810 ± 94	10903 ± 4.9	12876 ± 47	7621 ± 127	8645 ± 283	8773 ± 187
	Benzoylecgonine	1245 ± 26	1213 ± 37	1344 ± 41	1767 ± 45	1112 ± 33	1138 ± 32	1023 ± 11
	Norbenzoylecgonine	1120 ± 3.6	1310 ± 38	1491 ± 4.3	2093 ± 35	1321 ± 21	1195 ± 31	1048 ± 49
	Norcocaine	ND	ND	ND	ND	ND	ND	ND
	Cocaethylene	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	Anhydroecgonine methyl ester	ND	ND	ND	ND	ND	ND	ND
	Ecgonidine	ND	ND	ND	ND	ND	ND	ND
Amphetamine	Amphetamine	105 ± 18	98.8 ± 2.0	70.4 ± 0.4	102.0 ± 3.8	60.0 ± 1.6	77.7 ± 0.6	85.3 ± 2.2
Methamphetamine	Methamphetamine	17.3 ± 1.3	15.7 ± 0.0	14.2 ± 0.4	29.8 ± 0.9	14.5 ± 0.3	15.0 ± 0.5	13.3 ± 0.8
Methcathinone	Methcathinone	ND	ND	ND	ND	ND	ND	ND
BZP	BZP	ND	ND	ND	ND	ND	ND	ND
TFMPP	TFMPP	ND	ND	45.9 ± 0.6	95.9 ± 10.7	ND	81.7 ± 2.4	ND
Hallucinogens								
MDA	MDA	n/a	n/a	n/a	n/a	n/a	n/a	n/a
MDMA	MDMA	80.1 ± 3.3	70.2 ± 1.4	90.8 ± 3.1	392 ± 12.6	155 ± 5.4	163 ± 4.3	85.7 ± 1.0
MDEA	MDEA	ND	ND	ND	ND	ND	ND	ND
MBDB	MBDB	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	BDB	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Mescaline	Mescaline	ND	ND	ND	ND	ND	ND	ND
LSD	LSD	ND	ND	ND	ND	ND	ND	ND
	O-H-LSD	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Opiods and morphine derivatives								
Heroin	Heroin	ND	ND	ND	ND	ND	ND	ND
	6-acetylmorphine	487 ± 1.0	466 ± 19	1297 ± 25	623 ± 27	264 ± 18	302 ± 0.9	1025 ± 84
Codeine	Codeine	554 ± 9.0	563 ± 0.6	622 ± 6.2	535 ± 5.8	572 ± 25	587 ± 0.9	521 ± 7.2
	Norcodeine	213 ± 11	241 ± 12	234 ± 21	226 ± 11	214 ± 12	222 ± 17	228 ± 8.5
Oxycodone	Oxycodone	18.0 ± 0.8	20.3 ± 3.5	19.1 ± 2.9	20.2 ± 1.5	ND	ND	ND
	Oxymorphone	ND	30.9 ± 1.4	28.3 ± 1.1	27.6 ± 0.8	ND	28.9 ± 4.8	27.2 ± 3.0
Morphine	Morphine	n/a	n/a	n/a	n/a	n/a	n/a	n/a

	Normorphine	417	±	13	434	±	42	455	±	38	422	±	34	481	±	39	426	±	13	355	±	106
Dihydrocodeine	Dihydrocodeine	249	±	1.6	245	±	1.3	261	±	1.6	237	±	0.8	233	±	0.6	262	±	7.7	223	±	3.0
Buprenorphine	Buprenorphine	ND			ND			ND			ND			ND			ND			ND		
	Norbuprenorphine	ND			ND			ND			ND			ND			ND			ND		
Methadone	Methadone	80.5	±	1.1	84.7	±	0.1	90.7	±	0.6	85.7	±	1.5	78.0	±	0.8	86.1	±	1.3	79.9	±	1.3
	EDDP	113	±	6.0	110	±	1.8	118	±	4.0	109	±	2.4	104	±	0.1	127	±	1.1	112	±	8.5
	EMDP	ND			ND			ND			ND			ND			ND			ND		
Fentanyl	Fentanyl	ND			ND			ND			ND			ND			ND			ND		
	Norfentanyl	ND			ND			ND			ND			ND			ND			ND		
Propoxyphene	Propoxyphene	ND			ND			ND			389	±	2.4	ND			ND			ND		
	Norpropoxyphene	230	±	13	245	±	4.2	256	±	23	232	±	26	268	±	8.1	267	±	10	246	±	26
Tramadol	Tramadol	1150	±	18	1095	±	14	1052	±	17	990	±	22	1095	±	72	1115	±	17	976	±	51
	Nortramadol	897	±	173	885	±	118	890	±	80	1007	±	96	945	±	23	991	±	103	1023	±	168
Benzodiazepines																							
Temazepam	Temazepam	79.9	±	5.6	81.0	±	0.7	72.3	±	4.8	80.8	±	9.4	67.4	±	3.1	78.3	±	5.7	63.9	±	8.8
Diazepam	Diazepam	n/a			n/a			n/a			n/a			n/a			n/a			n/a		
	Nordiazepam	66.6	±	16	73.1	±	28	67.0	±	16	53.4	±	17	80.7	±	30	74.0	±	27	88.5	±	52
Nitrazepam	Nitrazepam	ND			ND			ND			ND			ND			ND			ND		
	7-aminonitrazepam	ND			ND			ND			ND			ND			ND			ND		
Oxazepam	Oxazepam	29.0	±	0.9	27.9	±	2.0	28.1	±	1.6	26.5	±	1.1	27.5	±	0.3	29.7	±	0.6	23.7	±	1.7
Chlordiazepoxide	Chlordiazepoxide	ND			ND			ND			ND			ND			ND			ND		
Antidepressants																							
Dosulepin	Dosulepin	84.6	±	2.8	113.2	±	13.7	110	±	10.3	112	±	8.3	112	±	17	126	±	8.2	116	±	22
Amitriptyline	Amitriptyline	1935	±	69	2342	±	320	2253	±	424	1855	±	521	2245	±	481	2455	±	197	1990	±	434
	Nortriptyline	127	±	12	111	±	22	96.0	±	20	76.6	±	18	88.0	±	27	117	±	18	89.6	±	27.4
Fluoxetine	Fluoxetine	88.4	±	4.5	104	±	10	105	±	2.8	81.4	±	0.9	112	±	13	113	±	3.7	82.3	±	9.3
	Norfluoxetine	51.3	±	0.4	48.2	±	14	43.2	±	7.9	48.7	±	20	68.8	±	12	74.7	±	3.6	43.5	±	19
Venlafaxine	Venlafaxine	1419	±	45	1396	±	23	1176	±	15	1045	±	5.9	1055	±	1.6	1418	±	29	1423	±	2.2
Dissociative anaesthetics																							
Phencyclidine	Phencyclidine	ND			ND			ND			ND			ND			ND			ND		
Ketamine	Ketamine	n/a			n/a			n/a			n/a			n/a			n/a			n/a		
	Norketamine	n/a			n/a			n/a			n/a			n/a			n/a			n/a		

Other																							
Methaqualone	Methaqualone	ND			ND			ND			ND			ND			ND			ND			
Sildenafil	Sildenafil	n/a			n/a			n/a			n/a			n/a			n/a			n/a			
Ephedrine	Ephedrine	n/a			n/a			n/a			n/a			n/a			n/a			n/a			
	Norephedrine	n/a			n/a			n/a			n/a			n/a			n/a			n/a			
Caffeine	Caffeine	796318.7	±	27459.6	777042.9	±	11171.7	731633.2	±	8216.4	674522.0	±	14215.4	649454.8	±	7593.4	792018.6	±	3082.6	770600.7	±	18469.7	
	1,7-dimethylxanthine	206231.3	±	2824.9	203942.5	±	843.1	180253.4	±	418.5	174266.4	±	1593.9	171421.2	±	726.7	202418.4	±	6988.3	197832.7	±	9410.7	
Nicotine	Nicotine	n/a			n/a			n/a			n/a			n/a			n/a			n/a			
	Continine	n/a			n/a			n/a			n/a			n/a			n/a			n/a			

Table 4 – Consumption of legal drugs using wastewater results and NHS data

Compound	DTR	Consumption estimates in local communities (mg day^{-1} 1000 people^{-1})	
		NHS data (2010)	Wastewater analysis (2010)
Opioids and morphine derivatives			
Codeine	Codeine	1946	565
	Norcodeine		225
Oxycodone	Oxycodone	54	20
	Oxymorphone		29
Dihydrocodeine	Dihydrocodeine	225	244
Methadone	Methadone	97	84
	EDDP		113
Propoxyphene	Norpropoxyphe.	47	249
Tramadol	Tramadol	1654	1068
Benzodiazepines			
Temazepam	Temazepam	54	75
Diazepam	Oxazepam	37	28
Antidepressants			
Dosulepin	Dosulepin	191	111
Amitriptyline	Amitryptyline	419	2154
	Nortriptyline		101
Fluoxetine	Fluoxetine	226	98
	Norfluoxetine		54
Venlafaxine	Venlafaxine	417	1276